TRANSDERMAL THERAPEUTIC SYSTEM CONTAINING HORMONES AND CRYSTALLIZATION INHIBITORS

The invention relates to a transdermal therapeutic system (TTS) for controlled release of oestradiol in combination with norethisterone acetate to the human skin.

Oestradiol in combination with norethisterone acetate has a very low saturation solubility in the auxiliaries normally used to formulate transdermal therapeutic systems, such as polyacrylate adhesives, tackifiers, plasticizers and absorption improvers. As a result, the capacity to load a TTS with dissolved active ingredient is greatly limited, and/or, in the case of supersaturation, unwanted crystallization occurs during storage. Consequently, the proportion of dissolved active ingredients in the matrix is reduced, which has an adverse effect on their release.

For combined preparations comprising oestradiol and norethisterone acetate, administration forms have been developed in which the active ingredients in a transdermal therapeutic system are contained in separate areas. However, manufacturing such TTSs is very expensive.

Accommodating drying agents together with transdermal therapeutic systems in the primary packaging reduces the risk of recrystallization but is far from straightforward.

DE-A 43 36 557 describes an active substance transdermal therapeutic system based on a pressure-sensitive adhesive which comprises rosin esters. It is prepared by kneading the components in the melt at temperatures between 100 and 140°C and then carrying out coating. Such high temperatures in the preparation of pharmaceutical forms carry with them the risk that degradation products may be formed in an unacceptably high amount.

WO 95/30409 describes a topical polymer release system for the administration of certain active ingredients by means of a propellantless aerosol pump. The absence of adhesives is emphasized as an advantage. Additional components used include crystallization inhibitors/ stabilizers and/or penetration enhancers such as substituted cyclodextrins, Transcutol, urea and isoterpenes; the active substance combination of oestradiol and norethisterone acetate is not claimed.

It is therefore an object of the invention to provide a stable, i.e. recrystallization-free, plaster comprising the active ingredients oestradiol and norethisterone acetate.

It has surprisingly been found that in a transdermal therapeutic system having the features of the main claim this object is achieved by the use of an amino-containing polymer as crystallization inhibitor. Advantageous crystallization inhibitors used are polymers based on butyl methacrylate, 2-dimethylaminoethyl methacrylate and methyl methacrylate, preferably in a molar ratio of 1:2:1, polyaminoamides, polyaminoimidazolines, polyetherurethaneamines, polyamines and polyglucosamines. It has been found that the crystallization inhibitors are particularly suitable in a proportion of from 0.05 to 30% by weight.

The formation of hydrogen bonds between the basic groups of the crystallization inhibitor and the mobile hydrogen atoms of the oestradiol molecule results in immobilization of oestradiol. Consequently, the concentration of freely mobile oestradiol in the matrix is reduced and crystallization prevented.

The pressure-sensitive adhesive reservoir contains oestradiol and norethisterone acetate in a weight ratio of from 1:2 to 1:15, preferably from 1:3 to 1:7, and in an overall concentration of up to 25% by weight.

The reservoir may comprise a constituent from the group consisting of ageing inhibitors, plasticizers, antioxidants and absorption improvers, the plasticizer being used in a concentration of from 0 to 5% by weight and the ageing inhibitor in a concentration of from 0.1 to 2% by weight.

Suitable ageing inhibitors, plasticizers, antioxidants and absorption improvers are known to the person skilled in the art and are described, for example, in DE 37 43 949.

In order to be able to apply the transdermal therapeutic system to the skin it is necessary for the system to have pressure-sensitive adhesive properties. In order to impart these properties to the transdermal therapeutic system of the invention use is made of polyacrylate pressure-sensitive adhesives in the form of solutions in organic solvents, known as solvent-based pressure-sensitive adhesives.

It is also possible to use polyacrylate pressure-sensitive adhesives in the form of aqueous dispersions.

Also suitable are hot-melt pressure-sensitive adhesives. These are free of solvent or dispersant and are applied from the melt.

UV-crosslinkable acrylate pressure-sensitive adhesives are also suitable. These are solvent-free and are applied using the conventional coating techniques. Subsequently, the polymer chains are crosslinked by irradiation with UV

light. This is necessary in order to give the pressure-sensitive adhesive adequate cohesion.

The reservoir of the transdermal therapeutic system may consist of a plurality of layers each with the same or different concentrations of active ingredient.

The layer thickness of the reservoir is from 0.02 mm to 0.500 mm but preferably from 0.030 mm to 0.200 mm.

The reservoir can be provided with an additional pressure-sensitive adhesive layer and/or with a pressure-sensitive adhesive margin. This becomes necessary when the pressure-sensitive adhesive properties of the reservoir itself are inadequate.

The transdermal therapeutic system of the present invention is intended for therapeutic applications in human medicine.

The invention is illustrated below on the basis of examples.

Example 1

155.08 g of Durotak 387-2287 (National Starch) (polyacrylate pressure-sensitive adhesive (PSA)) and
4.81 g of Eudragit E 100 (Röhm) (polyacrylate)

are homogenized with stirring and, together with a suspension of

2.17 g of Eutanol G (Caesar und Loretz) (long-chain fatty alcohol)
0.03 g of aluminium acetylacetonate (Merck-Schuchardt),
1.29 g of oestradiol hemihydrate and
8.33 g of norethisterone acetate,

are dissolved in a solvent mixture comprising

27.98 g   of ethyl acetate and
27.97 g   of ethanol.

The resultant adhesive solution is applied to a detachable protective layer of Hostaphan RN 100, siliconized on both sides, to give after drying an active substance matrix having a coated weight of 96.3 g/m^2. A backing layer impermeable to the active ingredients (0.015 mm thick polyester film) is laminated onto the resultant matrix. Subsequently, TTS patches measuring 40 cm^2 are punched out.

Examples 2-7 and comparison:

Preparation takes place as described under Example 1 but with the starting materials and amounts specified in Table 1.

Table 1: Composition [g]

Example	Comp-arison	2	3	4	5	6	7
Durotak 387-2287	424.31	132.84	162.25	171.50	171.50	162.25	171.50
Oestradiol hemihydrate	3.37	1.34	1.34	1.34	1.34	1.34	1.34
Norethister-one acetate	21.60	8.65	8.65	8.65	8.65	8.65	8.65
Eutanol G	5.59	2.25	2.25	2.25	2.25	2.25	2.25
Al acetyl-acetonate	1.36	0.054	0.054	0.054	0.054	0.054	0.054
Ethyl acetate		36.48	29.28	27.11	27.11	29.28	27.11
Ethanol		36.48	29.28	27.11	27.11	29.28	27.11
Methyl ethyl ketone	134.79	--	--	--	--	--	--
Euredur 145	--	20.0	--	--	--	--	--
Euredur 125	--	--	5.0	--	--	--	--
Euredur 250	--	--	--	0.5	--	--	--
Euredur 43	--	--	--	--	0.5	--	--
Euredur 27	--	--	--	--	--	5.0	--
Euredur 10	--	--	--	--	--	--	0.5

The test for signs of recrystallization was conducted microscopically in transmitted light at 40 tim s magnification. The results are set out in Table 2.

Table 2: Recrystallization

Example 1	Crystals per 40 cm^2 following storage for 3 months at 40°C
Comparison	154
1	0
2	0
3	0
4	0
5	0
6	0
7	0

As evident from Table 2 the addition of crystallization inhibitors gives transdermal therapeutic systems which are free from crystallization, in contrast to the comparative example (without crystallization inhibitor) in which there is considerable crystallization within a period of 3 months.

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